REMARKS

Claims 1-39 are pending in the instant application. Claims 1-32, 34, and 36, 37 and 39 are rejected. Claims 33, 35 and 38 are withdrawn from consideration.

Applicants appreciate that the last Amendment and Response was partially successful by overcoming the objection to the claims and the rejection under 35 USC 112, first paragraph. Applicants further appreciate the courtesy of a telephone interview with Applicants' representative, J. David Smith, on April 8, 2008. Applicants' representative presented new explanations not previously made of record and submitted the claims granted in the corresponding European Patent, EP 1 408 118. That is, the European Patent Office recognized that

> "By virtue of inclusion of step 5, which pertains to the extraction with solvent and subsequent crystallization of 4-O-β-D-galactopyranosyl-D-xylose, the Examining Division acknowledges novelty..."

and as regards "inventive step," the European Patent Office recognized that

> "The problem to be solved is to provide an improved enzymatic process in order to increase the proportion of 4-O-β-D-galactopyranosyl-D-xylose product with respect to the 2- and 3-O-β-D-galactopyranosyl-D-xylose products in the final mixture.
> ....
> The solutions proposed are the fractionation steps 5 and 6 of claim 1.
> ...
> The examples demonstrate that this results in a yield at 37°C of 71:29 (4-O-β-D-galactopyranosyl-D-xylose/ (2-O-β-D-galactopyranosyl-D-xylose)). No teachings are given in D1 or relevant prior art for that matter that would lead to the skilled person to modify the method of D1 employing said fractionation steps resulting in such high yield for 4-O-β-D-galactopyranosyl-D-xylose.
> ....
> Therefore, claims 1 to 37 are considered inventive."

See, Communication pursuant to Article 96(2) EPC, dated May 18, 2005, copy submitted herewith as Exhibit A.

The Examiner and the Examiner's supervisor both acknowledged that these new explanations represent significant progress. The Examiner was optimistic that no further data

would be required to establish the patentability of the present claims. The Examiner noted that the following explanations might help advance prosecution:

1. An explanation of any further products that are separated in the separation scheme and why it may be difficult to separate these products;
2. Referring to Example 1, an explanation of the ratios of the different sugar molecules;
3. Referring to Examples 1 and 2, an explanation of the solvents actually used and the amount of each one; and
4. Adding some recitations regarding the other products into the claims (*See*, paragraph [0047]), for example, a limitation regarding the relative proportions of the disaccharides produced, and an explanation of why this ratio is surprising.

In view of the foregoing, Applicants amend claim 1 to clarify that the method is "for producing 4-O-β-D-galactopyranosyl-D-xylose enzymatically in an amount at least 68% to 32% proportional to the amount of 2-O-β-D-galactopyranosyl-D-xylose and 3-O-β-D-galactopyranosyl-D-xylose combined." No issue of new matter arises by way of this amendment since express support for this ratio of 4:2+3 isomer is found in Table 1, paragraph [0049]. Applicants also change the "-" to "to" in referring to a percentage range in claim 1.

Rejection under 35 USC 103

Applicants previously submitted a signed, sworn Declaration of an inventor under 37 C.F.R. 1.312. However, the Examiner says that Crumpton *et al.* teach using an aqueous acetone for recrystallization of low molecular weight sugars. Further, while Applicants demonstrated in the Declaration that a purity of greater than 99% is achieved, the Examiner says that this would be expected in view of Crumpton *et al.* who teach that purifying low molecular weight sugar with aqueous acetone provides a product that is exceptionally pure. Further, the Examiner cites Schippers *et al.* as teaching that the optical purity and chemical purity are in close agreement.

1. *Reyes et al., U.S. Patent 5,994,092 in view of Ponpipom et al., U.S. Patent 4,228,274 and Crumpton et al., Biochem. J. 70(4):729 (1958)*

The Examiner maintains the rejection of claims 1-4, 21-24, 27-32, 34, 36, 37 and 39 as unpatentable over Reyes *et al.*, U.S. Patent 5,994,092 in view of Ponpiporn *et al.*, U.S. Patent 4,228,274 and Crumpton *et al.*, *Biochem. J.* 70(4):729 (1958) as before. In response to

Applicants' previous arguments, the Examiner says that Crumpton *et al.* teach using aqueous acetone for recrystallization. Further, the Examiner cites Schippers *et al.* as teaching that the optical purity and chemical purity are in close agreement.

2. *Reyes et al., U.S. Patent 5,994,092 in view of Ponpipom et al., U.S. Patent 4,228,274 and Crumpton et al., Biochem. J. 70(4):729 (1958) further in view of Wong-Madden et al., U.S. Patent 5,770,405 and Dahmen et al., U.S. Patent 4,675,392*

The Examiner maintains the rejection of claims 1, 5, 6 and 16-19 as unpatentable over Reyes *et al.*, U.S. Patent 5,994,092 in view of Ponpipom *et al.*, U.S. Patent 4,228,274 and Crumpton *et al.*, *Biochem. J.* 70(4):729 (1958) further in view of Wong-Madden *et al.*, U.S. Patent 5,770,405 and Dahmen *et al.*, U.S. Patent 4,675,392. The Examiner says that the solvent of Wong-Madden *et al.* is very similar to that of Reyes *et al.* Further, while Applicants' Declaration discusses economic and environmental advantages of the solvent of the present invention, the Declaration does not address whether the solvents of Wong-Madden *et al.* and Reyes *et al.* will separate oligosaccharides on an activated carbon column. According to the Examiner, one of ordinary skill in the art would recognize that the same solvent systems would work on both a silica gel column and an active carbon column. In addition, the Examiner says it would have been obvious to replace ethanol with isopropanol since they are equivalents as evidenced by Wong-Madden *et al.* Moreover, the Examiner says that the specifics of the solvent gradient and amount of activated carbon are merely optimized variables.

3. *Reyes et al., U.S. Patent 5,994,092 in view of Ponpipom et al., U.S. Patent 4,228,274 and Crumpton et al., Biochem. J. 70(4):729 (1958) further in view of Wong-Madden et al., U.S. Patent 5,770,405 and Dahmen et al., U.S. Patent 4,675,392 and further in view of Rao et al., Qual. Plant.-Pl. Fds. Hum. Nutr. XXVIII 4:293-303 (1979)*

The Examiner maintains the rejection of claims 1 and 7-15 as unpatentable over Reyes *et al.*, U.S. Patent 5,994,092 in view of Ponpipom *et al.*, U.S. Patent 4,228,274 and Crumpton *et al.*,

Biochem. J. 70(4):729 (1958) further in view of Wong-Madden *et al.*, U.S. Patent 5,770,405 and Dahmen *et al.*, U.S. Patent 4,675,392 and further in view of Rao *et al.*, Qual. Plant.-Pl. Fds. Hum. Nutr. XXVIII 4:293-303 (1979). According to the Examiner, it would be obvious that one could isolate sugars using either or a mixture of the recited elements. In addition, the Examiner says that it would be obvious to select other solvents or solvent mixes known to dissolve saccharides and to optimize the amounts of both solvent and celite. Still further, the Examiner says that the procedure for deactivating the column is also a matter of routine optimization.

4. *Reyes et al., U.S. Patent 5,994,092 in view of Ponpipom et al., U.S. Patent 4,228,274, Crumpton et al., Biochem. J. 70(4):729 (1958), Dahmen et al., U.S. Patent 4,675,392, Rao et al., Qual. Plant.-Pl. Fds. Hum. Nutr. XXVIII 4:293-303 (1979) and Wong-Madden et al., U.S. Patent 5,770,405 in further view of Gabelsberger et al., FEMS Leters 109(2-3): 131 (1993), Fujimoto et al., Glycoconjugate Journal 15:155 (1998) and Yoshitake et al., Eur. J. Biochem. 101:395 (1979).*

The Examiner maintains the rejection of claims 25 and 26 as unpatentable over this combination. According to the Examiner, it would have been obvious to one of ordinary skill in the art to use any of these three solvents in the phosphate buffer of Reyes *et al.* Further, the amounts recited represent mere optimization parameters according to the Examiner.

Applicants' Response

Applicants reiterate that the present invention provides an improved enzymatic process in order to increase the proportion of 4-O-β-D-galactopyranosyl-D-xylose product with respect to the 2- and 3-O-β-D-galactopyranosyl-D-xylose products in the final mixture. Applicants herein amend claim 1, and by virtue of dependency, all of the remaining claims, to clarify this point. The present invention provides fractionation steps (v) and (vi) of claim 1. The examples in the specification demonstrate that this results in a yield at 37°C of 71:29 (4-O-β-D-galactopyranosyl-D-xylose/ (2-O-β-D-galactopyranosyl-D-xylose)). *See*, Table 1. None of the cited prior art teaches or suggests adding the fractionation steps (v) and (vi) as recited in the currently pending claims. Even if, *assuming arguendo*, the prior art did teach such fractionation steps, the present invention would still be patentable because the prior art does not teach or suggest a process

resulting in such a high yield of 4-O-β-D-galactopyranosyl-D-xylose in proportion to the 2-O-β-D-galactopyranosyl-D-xylose and 3-O-β-D-galactopyranosyl-D-xylose. The patent law is clear that even a proper *prima facie* case of obviousness may be overcome by unexpectedly superior results or properties.

Applicants further submit that disaccharides 2-, 3-, and 4- are regloisomers (position isomers) having similar physical and chemical properties. Therefore, the separation of each isomer from the whole mixture is difficult since they share similar physical and chemical properties. *See, e.g.* Second Declaration under 37 C.F.R. 1.132 of Dr. Alfonso Fernandez-Mayoralas Alvarez, paragraphs 6 and 7. Yet, separating these isomers is very important because the 2- and 3- isomers do not work properly in an intestinal lactase test in which the 4- isomer is used.

The present invention provides a method for separating the isomers that the prior art does not teach or suggest. A surprisingly good 4:2+3 isomer ratio is achieved by the presently claimed process. This surprising ratio may be achieved due to the activity of the galactosidase enzyme of *E. coli*. The surprising ratio achieved ranges from 68:32 to 83:17 depending upon the temperature or pH conditions. When physiological conditions were used (37°C at pH 7.0), the ratio of 4:2+3 isomer was 71:29. An increased ratio of 4:2+3 isomer was observed when the temperature or the pH was lower than physiological conditions. *See*, Tables 1 and 2 of the instant specification. However, for many reasons, it may be preferable to use physiological conditions. Moreover, the purity of the 4-isomer separated by the presently claimed process was greater than 99%. *See, e.g.* Second Declaration under 37 C.F.R. 1.132 of Dr. Alfonso Fernandez-Mayoralas Alvarez, paragraph 10.

CONCLUSION

Entry of the foregoing amendments and remarks is respectfully requested. It is believed that all of the claims are in condition for allowance. If any issue can be resolved telephonically, the Examiner is invited to call the undersigned at the phone number provided.

Respectfully submitted,

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